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RELATIONSHIP BETWEEN TOXICITY VALUES FOR THE MILITARY POPULATION AND TOXICITY VALUES FOR THE GENERAL POPULATION

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The present chemical warfare agent toxicity estimates are not suitable for use with the general population (GP) because they are framed for male soldiers. A method was created to convert the median effective dose and Bliss slope to estimates applicable to the GP. It was assumed that individual susceptibilities have a log-normal distribution. Two mathematical models were developed to describe a healthy or sensitive subpopulation (SP). In the tail model, the SP consists of all individuals having susceptibilities within a tail of the GP distribution. In the bell model, the SP has a lognormal distribution. The median and the Bliss slope of an SP were determined as a function of the SP size. The two models gave similar results. Historical military demographics were used to estimate the size of the healthy SP from which military personnel are drawn. Uncertainty factors were obtained from the tail and bell models. Uncertainty factors from both models were consistent with the results of two previous studies that quantified differences between populations. Based on our analysis, revisions are required in the intraspecies uncertainty factors used in establishing proposed acute exposure guideline levels for threshold lethality due to inhalation of nerve agents.

14. SUBJECT TERMS

Toxicity	Subpopulations	Uncertainty Factors	Demographics	Probit Slope
Median Dosage	Concentration	Risk Assessment	CW Agents	Bell Model
Tail Model	Duration	Lognormal Distribution	Acute Exposure Guideline Levels	

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PREFACE

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1. INTRODUCTION

1.1 BACKGROUND

The U.S. Department of Energy's (DOE) Chemical and Biological Nonproliferation Program (CBNP) was initiated to improve the U.S. capability to prepare for and respond to the use of chemical and biological warfare (CBW) agents against civilian populations.[1] The Technology Development Program Area (Modeling Subgroup) within the CBNP is responsible for developing transport and dispersion models to be used for case studies and analyses. These models will be integrated into operational response planning and training, and consequence analysis tools. The models require estimates of human toxicity to CBW agents.[2,3] This report shows how to convert chemical warfare (CW) agent toxicity estimates established for military casualty estimation to estimates suitable for the general population.

1.2 CURRENT CW AGENT TOXICITY DATABASE

For chemical warfare (CW) agents, most of the available toxicological data and accompanying human toxicity estimates were generated in support of chemical weapon development and their offensive battlefield deployment.[4-8] The goal was to achieve lethality or incapacitation against military personnel on the battlefield, which at the time was nearly all male. As a result, available human toxicity data come from a limited segment of the overall population: relatively young, fit male soldiers with a mean mass of 70 kg.[4-6]

The present CW agent military toxicity estimates are not suitable for use with the general civilian population.[3-6] This is due to the population segment for which the estimates were developed and to the differences in philosophies between military and non-military risk assessment and management.

1.3 RISK ASSESSMENT

Risk assessment for the civilian population, including sensitive subpopulations (e.g., the elderly, the young, the chronically ill, etc.), has been geared toward setting "safe" exposure levels for sensitive individuals for *chronic* exposures.[7-10] This is often accomplished via the use of uncertainty factors, which account for the paucity of data and uncertainty inherent in extrapolation.[5,7-20] Factors between 1 and 10 are typically used to account for each source of uncertainty.[7-10,17] Using an uncertainty factor of 10 for, say, animal-to-human extrapolation means assuming that humans are 10 times more sensitive than laboratory animals. An uncertainty factor is simply a guess at an unknown conversion factor, with a margin of safety included.

Most toxicity data on noncarcinogenic and nonmutagenic chemicals were collected to address chronic effects from long-term or lifetime daily exposures, and uncertainty factor (UF) methodology was developed for such data.[10] Acute exposures involving high concentrations may not be satisfactorily addressed by an UF methodology based on chronic exposures. Data indicate that there may be less response variability among individuals subjected to acute exposures, as opposed to chronic exposures; thus, appropriate UFs for acute exposures may be smaller.[10]

Acute exposure limits, such as Acute Exposure Guideline Levels (AEGL)[10] established to accord sufficient protection to the sensitive subpopulation, are useful for transport and dispersion models, which make predictions of agent concentration as a function of ground location and time after release. Exposure limits can be used to map out ground locations where concentrations are sufficient to produce a stated effect on a sensitive individual. Such predictions are valuable for civil defense purposes (such as identification of populated areas that are at risk from an industrial accident and planning evacuation routes), but they do not provide casualty estimates. To estimate casualties, the median effective dosage and the probit slope must be known.

In contrast to civilian scenarios, in which safety is paramount, for military operations both over- and under-estimation of CW agent toxicity are to be avoided.[6] Underestimation may lead to the provision of insufficient protection of the soldier from CW agent exposure. Overestimation can lead to overly burdensome protective measures, which can produce casualties as well (e.g., heat injuries from the prolong wearing of protective clothing). Thus, military risk assessment for CW agent exposures must involve the assessment of both the benefits and liabilities associated with protection against CW agents. The goal is to successfully accomplish the mission while keeping military casualties from all causes to a minimum. To achieve this, reliable estimates of military casualties are necessary.

Even for the civilian population, there are exposure scenarios in which the overestimation of toxicity is not desirable. Toxicity values influence risk management decisions with respect to whether civilians should evacuate or shelter-in-place in response to a release of toxic chemicals.[9,10,21-23] The use of CW agents against the general population by terrorists (a scenario of interest to the CBNP) falls into this type of exposure category.

This report investigates what the uncertainty factor should be for the extrapolation of toxicity estimates from a healthy subpopulation to the general population. Furthermore, it is the difference between the two groups with respect to their median response and probit slope that is of primary interest, since it is these two parameters that are used by transport & dispersion[24] and hazard assessment[25] models when making casualty estimates.[5-6,23,25-29] Thus, the conversion of the median effective dosage and the probit slope for a healthy subpopulation to estimates for the general population will allow these models to make casualty estimates for the general population.

2. THEORY

2.1 RESPONSE DISTRIBUTION STATISTICS

For each individual, there is a dose or dosage* that is just sufficient to produce a specified biological response. These just-sufficient dosages are called effective dosages to distinguish them from administered dosages. The distribution of effective dosages for a homogeneous population is usually lognormal.[3,5,14,16,17,26,29-41] A lognormal distribution of effective dosages is expected when:[37,38,41-43] (1) there are many factors contributing to the overall variability in the population; (2) no one or two factors are dominant contributions to the overall variability; (3) an individual's susceptibility to the toxicant is the product of the contributing factors; and (4) any interactions among the contributing factors are minimal.

* The terms dose and dosage are often used interchangeably, but they do have different definitions. Dose is the total amount of a substance that is administered, while dosage is an amount administered relative to some other quantity (e.g., body mass, body surface, and/or time).[30] For inhalation exposures, dosage is the term used.[5,8,25,26,30,31] For simplicity, only the term "dosage" will be used, but the method developed in this report is applicable to both dose and dosage units.

Important exceptions occur when any of these conditions are not met; such exceptions typically result in mixed distributions or normal distributions.[43]

A plot of the density function, Φ, for the normal distribution of log(effective dosage) produces the well known bell-shaped curve.[43-46] The two parameters most often used to characterize a normal distribution are its mean μ and variance σ^2 (or standard deviation σ).[46] Using these two parameters, every normally distributed random variable X can be standardized to a standard normal random variable Z:

$$Z = \frac{(X - \mu)}{\sigma}. \qquad [1]$$

In toxicology, X is usually the logarithm of the dosage.

Although statisticians typically describe the lognormal distribution of effective dosages by the mean and variance of log(effective dosage), toxicologists usually describe the distribution by the median effective dosage, ED_{50}, and the probit (or Bliss) slope, m:

$$ED_{50} = \text{antilog}(\eta) \qquad [2]$$

$$m = 1 / \sigma \qquad [3]$$

where η is the median of log(effective dosage). The median effective dosage, ED_{50}, is the dosage at which 50% of the exposed individuals will exhibit a specified biological response. For vapor exposures, the equivalent dosage term is the 50% effective concentration (EC_{50}) or the product of the exposure concentration and exposure time (ECT_{50}).[5,30] Median effective dosages are in the original units, not in logarithms of the original units, and hence are easier to interpret than μ. Although the mean μ and median η of a normal distribution are the same ($\mu = \eta$), this property does not hold for a lognormal distribution.

Effective dosages for response levels other than 50% can be calculated from μ and σ, by solving for X in [1] and using the Z value corresponding to the cumulative probability of interest. The 50% response level corresponds to a Z value of zero. Tables of cumulative probabilities and their corresponding Z values are found in standard statistical textbooks[44,46-48] or obtained using statistical software.[49]

Toxicologists traditionally use base 10 logarithms to calculate the probit (Bliss) slope.[5,6,31-39] We will follow the toxicological tradition of using base 10 logarithms. Probit slopes based on both natural and base 10 logarithms are found in the literature. Care must be exercised when comparing probit slopes from different sources.

The probit slope equals the number of standard deviations (ΔZ) corresponding to a factor of 10 change in effective dosage (ED).[5] Thus, a probit slope of six means that a factor of 10 change in ED corresponds to six standard deviations ($\Delta Z = 6$). For the normal distribution, a range of Z from negative four (very sensitive individuals) to four (highly tolerant individuals) (or $\Delta Z = 8$) encompasses over 99.99% of the total population. If the toxicant has a probit slope of eight, a factor of 10 separates the effective dosages for these two Z values. The higher the probit slope the closer the two tails of the distribution are in terms of ED (in other words, there is less variance in the effective dosages of the population).

Though the normal distribution is continuous, quantal data (response versus no response) are used to estimate the parameters (median and probit slope) of the distribution of effective dosages.[36,37] Probit analysis and maximum likelihood estimation (MLE) are used to estimate these parameters from data.[36,50] The following equation is fitted via probit analysis/MLE for vapor toxicity studies: [36,50]

$$Y_N = (Y_P - 5) = k_0 + k_1 \log C + k_2 \log T, \quad [4]$$

where Y_N is a normit, Y_P is a probit, and the k's are fitted coefficients, C is vapor concentration, and T is exposure time. The constants k_1 and k_2 are the probit slopes for concentration and time, respectively. Often, experiments are conducted with exposure time held constant, which reduces [4] to the traditional probit equation.[36] Thus, the probit slope for a vapor exposure usually refers to the slope on vapor concentration ($m = k_1$) instead of the slope on exposure duration. Some studies report a probit slope for a term combining C and T (the toxic load, $C^n T$, with n being the toxic load exponent).[25-27,29,50-53] Thus, for comparison with other studies, probit slopes reported for a toxic load will be converted to probit slopes for C.

When fitting [4], all variability in the data will contribute to the estimate for m, be it from variance due to individual susceptibilities, batch effects, experimental error, etc. Probit analysis performed on a compilation of data from many sources will not produce an accurate measure of variance among individuals due to the heterogeneity introduced by differences among the studies (e.g., experiment procedures, type of animals used, etc.).[51] The effect of such heterogeneity will be to lower the probit slope.

2.2 PREVIOUS WORK IN ESTIMATION OF UNCERTAINTY FACTORS

Traditionally, an UF of 10 has been used for extrapolation from healthy humans to sensitive humans. However, the original development of this UF value was not based on any human observations[10,39] and the arbitrary setting of an UF equal to 10 may be inappropriate.[10,38,39] This can be demonstrated by calculating either the ratio of the 95th to the 5th percentile or the ratio of the 99th to the1st percentile of the lognormal distribution of effective dosages.[38] The ratio only equals 10 when the probit slope of the general population equals 3.29 or 4.65, respectively. Steeper probit slopes give lower ratios. Table 1 gives ratios of the 90th to the 10th percentile, the 95th to the 5th percentile, and the 99th to the 1st percentile of a lognormal distribution as a function of probit slope.

In estimating the degree of variability among humans, the emphasis of the risk assessment community has been to focus on only one human population distribution—that of the general population. The distance between the two tails has been used to help define the UF for extrapolation from healthy to sensitive humans. However, the problem in applying this work to CW agent toxicity is that there are currently no estimates for the probit slope for the general population. The emphasis in CW agent toxicity research has been to derive distribution parameters (median and probit slope) for a healthy subpopulation (the military).

We expect that the probit slope for a subpopulation will be greater (indicating less variance) than the probit slope for the general population. However, a literature search did not find any work that investigated how the probit slope of the general population can be estimated from a known subpopulation probit slope.

Table 1. Ratios of Percentiles

Probit Slope	Ratio of Percentiles		
	90th to 10th	95th to 5th	99th to 1st
30.00	1.22	1.29	1.43
25.00	1.27	1.35	1.53
20.00	1.34	1.46	1.71
15.00	1.48	1.66	2.04
12.00	1.64	1.88	2.44
10.00	1.80	2.13	2.92
9.00	1.93	2.32	3.29
8.00	2.09	2.58	3.82
7.00	2.32	2.95	4.62
6.90	2.35	3.00	4.72
6.00	2.67	3.53	5.96
5.00	3.26	4.55	8.52
4.65	3.56	5.10	10.0
4.00	4.37	6.64	14.6
3.29	6.01	10.0	26.0
3.00	7.15	12.5	35.6
2.50	10.6	20.7	72.6
2.00	19.1	44.1	212
1.50	51.1	156	1264
1.00	366	1949	44945

2.3 SUBPOPULATION MODELS

We model the susceptibility of the general population (also called the whole population to distinguish it from various subpopulations) to CW agents by a lognormal distribution of effective dosages. We standardize the normal distribution of log(ED) by [1] so that the general population has a normal distribution with mean zero and variance one in our model. The units of this distribution are called Z units of the general population and most calculations are done in these units; the results are converted to an ED_{50} and a probit slope.

One might consider the age, health, and physical fitness status of military personnel as irrelevant to their susceptibility to CW agents. Then the military population can be treated as a random sample of the general population. This viewpoint yields a conversion factor of one for both the median and the probit slope. Alternatively, both sensitive and healthy groups

can be viewed as non-random samples from the general population. We model these groups as subpopulations. The relationships between the medians and between the probit slopes of the subpopulation and the general population can be determined mathematically. We considered two models to represent either a healthy or a sensitive subpopulation: the tail model and the bell model.

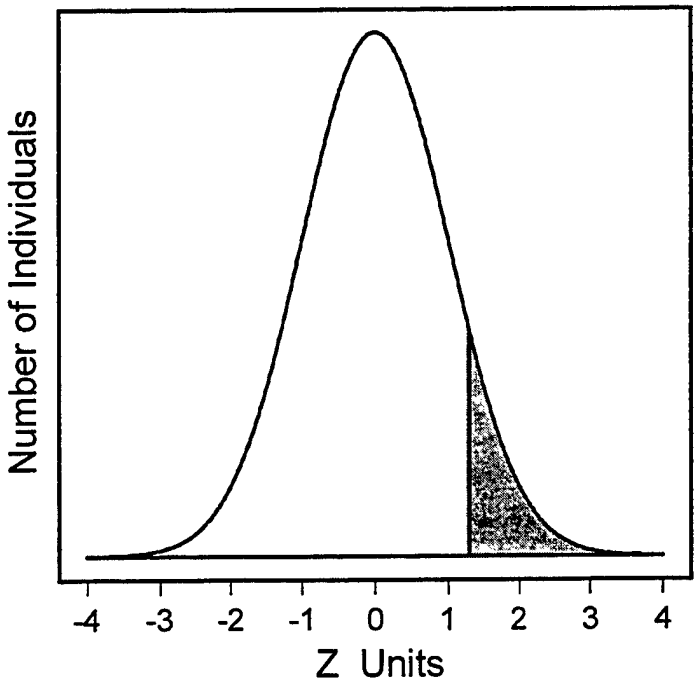
2.3.1 Tail Model

In the tail model, the subpopulation consists of those individuals having effective dosages within a tail of the general population. The size of the subpopulation, θ, is defined as a fraction of the general population, and the boundary of the tail, a, is given (in Z units of the general population) by:

$$a = G(1 - \theta) \text{ (for healthy) or } G(\theta) \text{ (for sensitive)}, \quad [5]$$

where G is the inverse cumulative distribution function of a standard normal variable. Figure 1 shows the healthiest 10% of the general population (a = 1.28 is the tail boundary).

Figure 1. Tail Model for a Healthy Subpopulation



The mean and variance of the tail region (in Z units of the general population) are[54]

$$\mu_{tail} = \pm \Phi(a)/\theta \quad [6]$$

and

$$\sigma^2_{tail} = 1 \pm a\left[\frac{\Phi(a)}{\theta}\right] - \left[\frac{\Phi(a)}{\theta}\right]^2 = 1 \pm a\mu_{tail} - \mu^2_{tail}, \qquad [7]$$

where a is the border of the tail region. In [6] and [7], the ± is plus for a healthy subpopulation and minus for a sensitive subpopulation.

The probit slope of the tail subpopulation, m_{tail}, is $1/\sigma_{tail}$. Note that m_{tail} is still the number of standard deviations (ΔZ) corresponding to a factor of 10 change in effective dosage; however, Z units of a tail subpopulation cannot be transformed into cumulative percent for the subpopulation by using a normal distribution.

We can find the median of the subpopulation in Z units of the general population. The healthy subpopulation median is the $[100\ (1 - \theta_{tail}/2)]^{th}$ percentile of the general population and the sensitive subpopulation median is the $[100\ (\theta_{tail}/2)]^{th}$ percentile of the general population. Hence, in Z units of the general population, η_{tail} is:

$$\eta_{tail} = G\left(1 - \frac{\theta_{tail}}{2}\right) \text{ (for healthy) or } G\left(\frac{\theta_{tail}}{2}\right) \text{ (for sensitive)} \qquad [8]$$

The percentiles, ψ_{tail}, of the tail subpopulation are related to the percentiles of the whole population, ψ_{whole}, by:

$$\psi(XX)_{tail} = \psi(100 - \theta\ (100 - XX))_{whole} \qquad \text{(for healthy)} \qquad [9a]$$

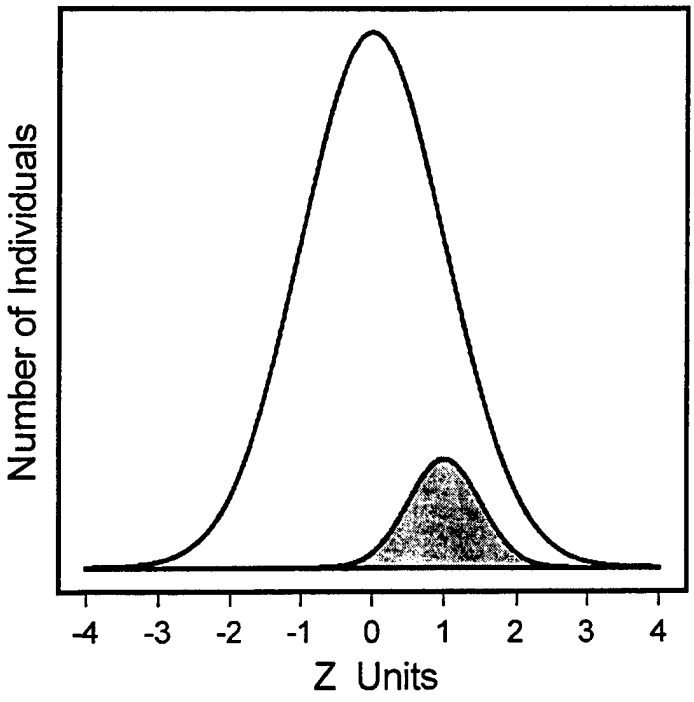
$$\psi(XX)_{tail} = \psi(\theta\ XX)_{whole} \qquad \text{(for sensitive)} \qquad [9b]$$

2.3.2 Bell Model

In the bell model, the subpopulation has the same type of distribution as the general population—the distribution of the logarithm of effective dosage is normal. Thus, the subpopulation is represented as a small bell within the larger bell of the general population. Figure 2 shows a subpopulation ($\mu_{bell} = 1$, $\sigma_{bell} = 0.5$) that is 10% of the whole population. Not every individual in the upper tail of the general population is in the military—which is what the tail model assumes. Instead, the assumption of the bell model is that the effective dosages for individuals in the military are represented by a lognormal distribution.

Unlike the tail model, specifying the size of the subpopulation, θ, in the bell model does not determine the mean, μ_{bell}, or the standard deviation, σ_{bell}, of the subpopulation. For the bell model, the distribution for a healthy subpopulation was moved as far as possible to the upper end of the general distribution [the bell curve of the subpopulation must remain entirely within (or under) the bell curve of the general population]. However, the distance that the subpopulation can be shifted depends on σ_{bell}. Thus, for selected values of θ, we found (by a numerical search) values for σ_{bell} that yielded the largest possible difference between the medians of the subpopulation and the general population.

Figure 2. Bell Model for a Healthy Subpopulation



The percentiles, ψ_{bell}, of a bell subpopulation are:

$$\Psi(XX)_{bell} = \mu_{bell} + G\left(\frac{XX}{100}\right)\sigma_{bell}, \qquad [10]$$

where ψ_{bell}, μ_{bell}, and σ_{bell} are in Z units of the whole population.

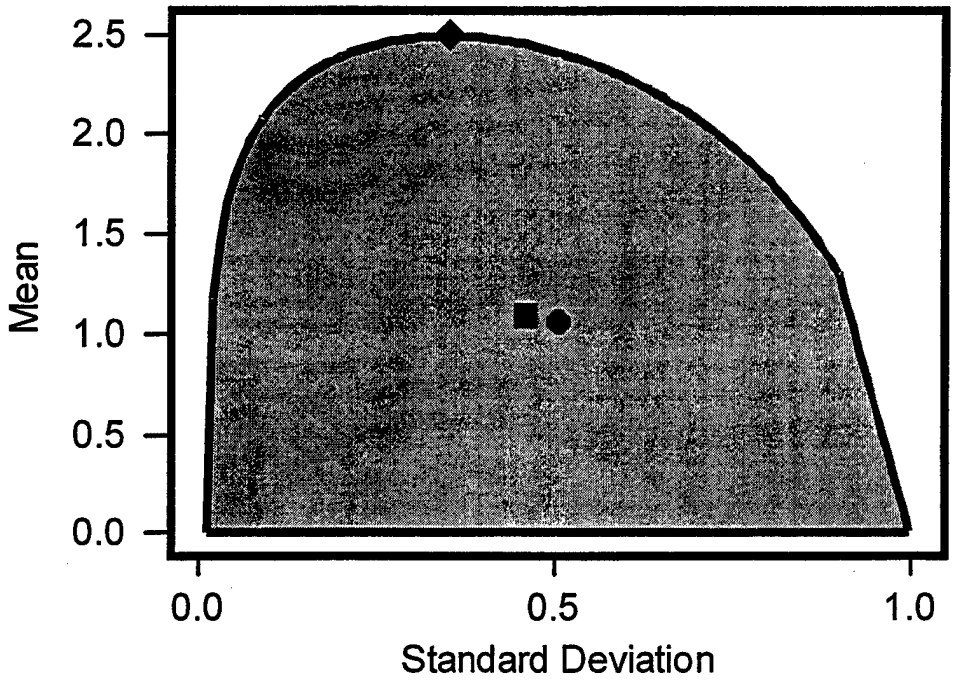
2.3.3 Other Models, Gender, Mixed Distributions, and CW Agents

In the bell model, the standard deviation of the subpopulation is selected to achieve the greatest shift of the subpopulation median away from the general population median. Different results would be obtained if the standard deviation were selected to maximize the shift of some other percentile (instead of the median). Distributions other than the lognormal can be used to model a subpopulation. However, such complications are unnecessary. The tail model provides the most extreme results for every percentile. Thus, the uncertainty factor for any percentile is bounded between one (obtained from the viewpoint that the subpopulation is a random sample from the general population) and the uncertainty factor given by the tail model. The motivation for developing the bell model was to obtain more reasonable estimates than those of the tail model. However, the bell model is still conservative (in the sense of yielding large uncertainty factors for percentiles) due to the maximization of the shift of the median of the subpopulation.

Yet, it is not a requirement that σ_{bell} and μ_{bell} be chosen to achieve a maximum shift in the median. A two-dimensional parameter space exists of feasible σ_{bell} and μ_{bell} values where the subpopulation curve will remain entirely within or under the general population curve. Figure 3 shows the feasible region (shaded) for a healthy subpopulation of size $\theta = 0.01$ (or

1%). The diamond at the top of the shaded region marks the σ_{bell} and μ_{bell} coordinates for the largest possible median shift.

Figure 3. Feasible Region for σ_{bell} and μ_{bell} of a Healthy Subpopulation of Size 1%.



The centroid[56] of the feasible region was found by numerical integration (using Simpson's Rule),[55,56] and is denoted by a square in Figure 3. Approximating the feasible region by a semi-circle allows the centroid to be estimated by[56]

$$\sigma_{centroid} = (\theta + 1) / 2 \qquad [11]$$

and

$$\mu_{centroid} = (4 / 3\pi)\ \mu_{max} = (0.4244)\ \mu_{max}, \qquad [12]$$

where μ_{max} is the maximum possible value of μ_{bell} (worst case scenario) for the specified θ. The circle in Figure 3 indicates the semi-circle approximation of the centroid.

Centroid estimates from the semi-circle approximation are in good agreement with values obtained from numerical integration (Table 2). The agreement is better for large θ than for small θ. The semi-circle formulas can be used to obtain estimates that are less conservative than the worst-case combination of σ_{bell} and μ_{bell}. However, in the rest of this report, we use the worst-case combination of σ_{bell} and μ_{bell}, so μ_{bell} equals μ_{max}.

The subpopulation models developed in this report assume that the distribution of effective dosages within the general population is lognormal. In general, this assumption holds true, but there are some cases where mixed distributions are encountered.[43,57,58] Gender is a factor commonly associated with the occurrence of mixed distributions.[43]

Table 2: Estimation of Centroid of Feasible Region for σ_{bell} and μ_{bell}

Subpop. Size (%)	Centroid Calculation Method			
	Numerical Integration		Semi-Circle Formula	
	$\sigma_{centroid}$	$\mu_{centroid}$	$\sigma_{centroid}$	$\mu_{centroid}$
1	0.458	1.089	0.505	1.061
25	0.618	0.450	0.625	0.450
90	0.950	0.043	0.950	0.042

For CW agents, there is evidence to suggest the possible existence of mixed distributions due to the presence of gender effects in both human[7,8] and animals.[31,32,59-62] There is not enough evidence to confirm whether factors other than gender will produce a mixed distribution of effective dosages for CW agents.[63]

A mixed distribution due to gender effects can be analyzed by applying the subpopulation models to each gender separately. Thus, two conversions will be performed: healthy male subpopulation to general male population, and healthy female subpopulation to general female population.

2.4 HEALTHY SUBPOPULATION SIZE ESTIMATION

The uncertainty factor method proposed in this report is dependent on an estimate of the size of the subpopulation of interest. The vast majority of historical human CW agent research involved healthy male soldiers. Thus, the conversion of the present human CW agent toxicity estimates to estimates for the general population requires a size estimate for the military subpopulation. Currently, the percentage of the population serving in the military is small. However, we view individuals currently in the military as being a random sample from a much larger pool of healthy individuals. For the subpopulation models, we need an estimate of the size of this pool of healthy individuals. One approach for obtaining such an estimate is to examine U.S. demographics during World War II.

In World War II, the United States had a peak military strength of 12.1 million (in 1945), and the total number of military personnel over the course of the war was 16.3 million.[64] The population of the United States was 140 million in 1945.[65] Therefore, about 8.6% (12.1/140) of the U.S. population in 1945 was in the military, the vast majority of which were male. This implies that 17% of U.S. males were in the military in 1945. Besides the healthy U.S. males in the World War II military, there were other males who were healthy enough for military service but did not serve. Thus, 17% is a lower bound for θ_{hm}, the size of the healthy male subpopulation.

U.S. men in age from 18 to 45 years old were liable for service in World War II.[66] This age group now comprises about 40% of the total male population.[67] However, not every man in this group is healthy enough for military service. Thus, 40% is an upper bound for θ_{hm}. A reasonable estimate for θ_{hm} is 25% of the male population. Because resistance to CW agents

is not necessarily a function of physical strength and size, the healthy female population can be assumed to be the same size as the healthy male population, or 25% of the female population. The estimate (25%) of the size of the healthy subpopulation applies to the subpopulation from which military personnel are drawn. There are other healthy subpopulations, such as the working population. Subpopulations must be clearly defined to get appropriate estimates of their size.

2.5 ESTIMATION OF HUMAN VARIABILITY

For CW agent toxicology, variability within the human population has been estimated from animal studies and from non-lethal human studies. Historically, both types of studies involved a healthy subpopulation. The probit slope obtained from animal studies may be higher than that from human studies, due to the greater homogeneity found within inbred laboratory animals.[5] However, if an individual's health (rather than genetics) is the dominant factor affecting susceptibility, there may be little difference in probit slopes between a healthy animal population and a healthy human population. Thus, for comparison with previous studies, we assume that animal probit slopes are equivalent to the probit slope of the healthy (military) human subpopulation.

2.6 CALCULATION OF UNCERTAINTY FACTORS

Given a probit (Bliss) slope for the general population, the uncertainty factor for any percentile ψ between a subpopulation and the whole population is

$$UF = \text{antilog}\left(\left| \psi_{sub} - \psi_{whole} \right| / m_{whole} \right), \qquad [13]$$

where the percentiles are in Z units of the whole population. The use of the absolute value of $\psi_{sub} - \psi_{whole}$ (indicated by the bars | |) in [13] makes the UF greater than one, but also makes the use of the UF (as a multiplier or divisor) dependent on the application. Whether to multiply or divide by the UF depends on whether the subpopulation is sensitive or healthy, and on whether the conversion is general population to subpopulation or vice versa.

The UF for the median between a subpopulation and the whole population can be calculated using a modified [13], since η_{whole} equals zero:

$$UF = \text{antilog}\left(\left| \eta_{sub} \right| / m_{whole} \right), \qquad [14]$$

where the subpopulation median is in Z units of the whole population.

An uncertainty factor can be obtained for differences between two subpopulations (e.g., healthy to sensitive). In which case, a modified [13] is used (with ψ expressed in Z units of the whole population):

$$UF = \text{antilog}\left(\left| \psi_{sub1} - \psi_{sub2} \right| / m_{whole} \right) \qquad [15]$$

3. RESULTS

3.1 SUBPOPULATION STATISTICS

Calculated standard deviations, Bliss slopes, means, medians, and 1st percentiles for sensitive and healthy subpopulations are presented in Tables 3 (tail model), and

4 (bell model); these statistics are function of the subpopulation size, which is listed as a percent of the whole population in Tables 3 and 4.

Table 3. Tail Model Statistics

Subpop. Size (%)	Standard Deviation	Bliss Slope	Healthy			Sensitive		
			Mean	Percentile		Mean	Percentile	
				50	01		50	01
1	0.31	3.21	2.67	2.58	2.33	-2.67	-2.58	-3.72
3	0.35	2.87	2.27	2.17	1.89	-2.27	-2.17	-3.43
5	0.37	2.69	2.06	1.96	1.65	-2.06	-1.96	-3.29
10	0.41	2.43	1.75	1.64	1.29	-1.75	-1.64	-3.09
15	0.44	2.27	1.55	1.44	1.04	-1.55	-1.44	-2.97
20	0.47	2.14	1.40	1.28	0.85	-1.40	-1.28	-2.88
25	0.49	2.03	1.27	1.15	0.68	-1.27	-1.15	-2.81
30	0.51	1.94	1.16	1.04	0.53	-1.16	-1.04	-2.75
35	0.54	1.86	1.06	0.93	0.39	-1.06	-0.93	-2.70
40	0.56	1.79	0.97	0.84	0.26	-0.97	-0.84	-2.65
45	0.58	1.72	0.88	0.76	0.14	-0.88	-0.76	-2.61
50	0.60	1.66	0.80	0.67	0.01	-0.80	-0.67	-2.58
60	0.65	1.54	0.64	0.52	-0.24	-0.64	-0.52	-2.51
70	0.70	1.42	0.50	0.39	-0.50	-0.50	-0.39	-2.46
80	0.76	1.31	0.35	0.25	-0.81	-0.35	-0.25	-2.41
90	0.84	1.19	0.19	0.13	-1.23	-0.19	-0.13	-2.37
100	1.00	1.00	0.00	0.00	-2.33	0.00	0.00	-2.33

The units for the standard deviations, means, and percentiles in Tables 3 and 4 are Z units of the whole population; the Bliss slope is the reciprocal of the standard deviation (SD). The standard deviation and Bliss slope apply to both healthy and sensitive subpopulations of the specified size. For the bell model, the mean is the 50^{th} percentile.

Figure 4 shows the median of a healthy subpopulation (given in Z units of the whole population) as a function of subpopulation size (given as percent of the whole population). There is little difference between the tail and bell models; the subpopulation median is primarily a function of the subpopulation size. Figure 5 gives the ratio of probit slopes between a subpopulation and the whole population (m_{sub} / m_{whole}). This ratio is dependent on only the size of the subpopulation and the model used.

Table 4. Bell Model Statistics

Subpop. Size (%)	Standard Deviation	Bliss Slope	Healthy Percentile		Sensitive Percentile	
			50	01	50	01
1	0.35	2.84	2.50	1.68	-2.50	-3.32
3	0.40	2.49	2.09	1.15	-2.09	-3.02
5	0.43	2.31	1.87	0.86	-1.87	-2.88
10	0.49	2.04	1.55	0.42	-1.55	-2.69
15	0.53	1.88	1.35	0.11	-1.35	-2.59
20	0.57	1.76	1.19	-0.13	-1.19	-2.51
25	0.60	1.66	1.06	-0.34	-1.06	-2.46
30	0.63	1.58	0.95	-0.53	-0.95	-2.42
35	0.66	1.51	0.85	-0.70	-0.85	-2.39
40	0.69	1.45	0.76	-0.85	-0.76	-2.36
45	0.72	1.39	0.67	-1.00	-0.67	-2.34
50	0.75	1.34	0.60	-1.14	-0.60	-2.33
60	0.80	1.25	0.46	-1.40	-0.46	-2.31
70	0.85	1.18	0.33	-1.65	-0.33	-2.30
80	0.90	1.11	0.21	-1.88	-0.21	-2.31
90	0.95	1.05	0.10	-2.11	-0.10	-2.31
100	1.00	1.00	0.00	-2.33	0.00	-2.33

Figure 4. Median Versus Subpopulation Size. Solid line for tail model; dashed line for bell model; dotted line for semi-circle centroid.

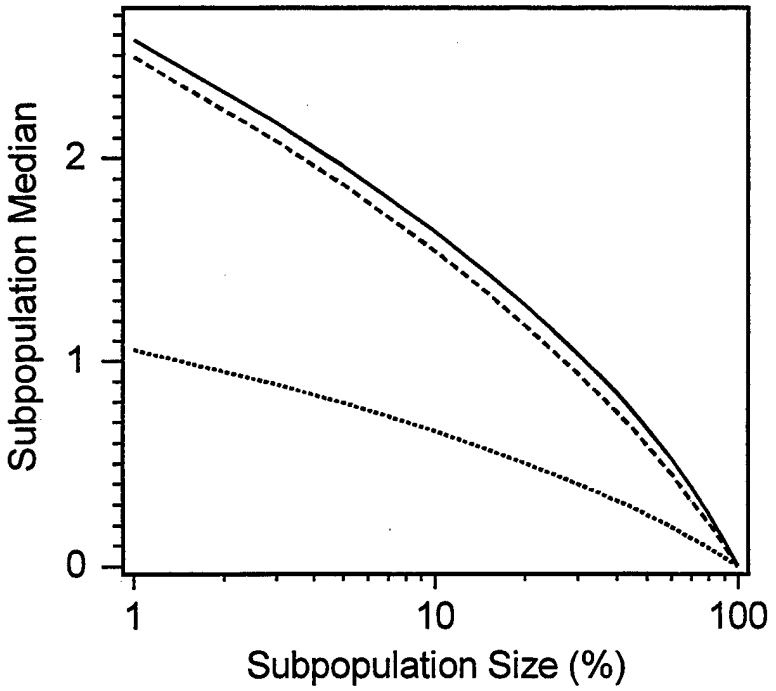
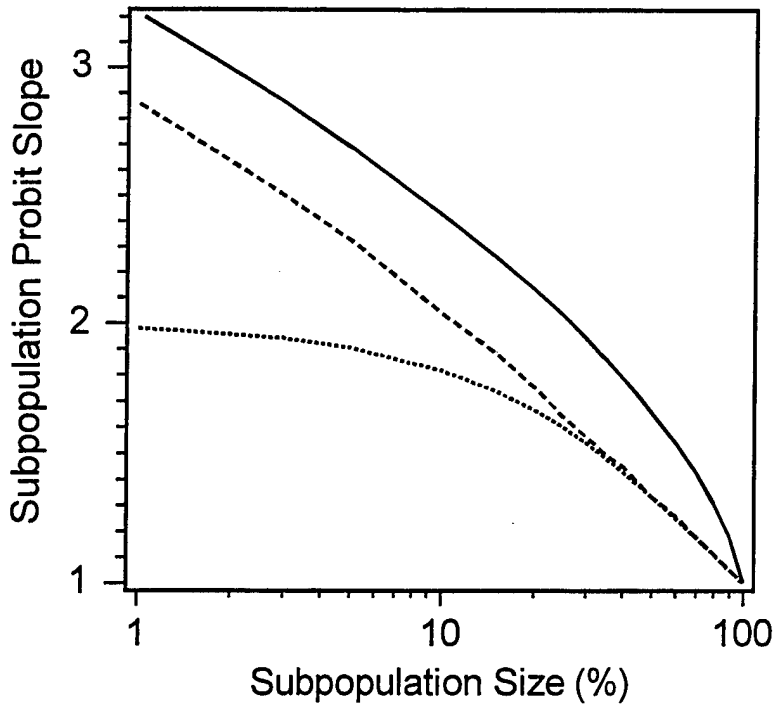


Figure 5. Probit Slope Versus Subpopulation Size. Solid line for tail model; dashed line for bell model; dotted line for semi-circle centroid.



3.2 UNCERTAINTY FACTORS FOR THE MEDIAN

The UFs were calculated based on η_{sub} using [14] for both the tail and bell models. The results for the tail model are presented in Figure 6 and tabulated in Table 5; for the bell model, the results are presented in Figure 7 and tabulated in Table 6. The UFs were calculated as a function of both m_{whole} (from 2 to 20) and θ_{sub} (from 1% to 100% of the whole population).

3.3 UNCERTAINTY FACTORS FOR THE 1st PERCENTILE

Sometimes risk assessment is performed using the first percentile.[9,10] Thus, the UFs were calculated based on $\psi(01)_h$ and $\psi(01)_{whole}$ using [13] for both the tail and bell models. The results for the tail and bell models are tabulated in Tables 7 and 8, respectively. The UFs were calculated as a function of both m_{whole} (from 2 to 20) and θ_h (from 1% to 100% of the whole population). These UFs apply to the conversion of the first percentile of a healthy subpopulation to the first percentile of the general population; they cannot be used for conversions between the general population and a sensitive subpopulation.

4. DISCUSSION

4.1 SAMPLE CALCULATIONS

We give the following example of the method to show the procedure; the resulting toxicity estimates are not to be construed as a recommended or officially approved toxicity estimates for the exposure scenario or subject population mentioned in the example.

Figure 6. Uncertainty Factor for Median — Tail Model. Whole population probit slopes: 2, 3, 4, 5, 6, 8, 12, 20.

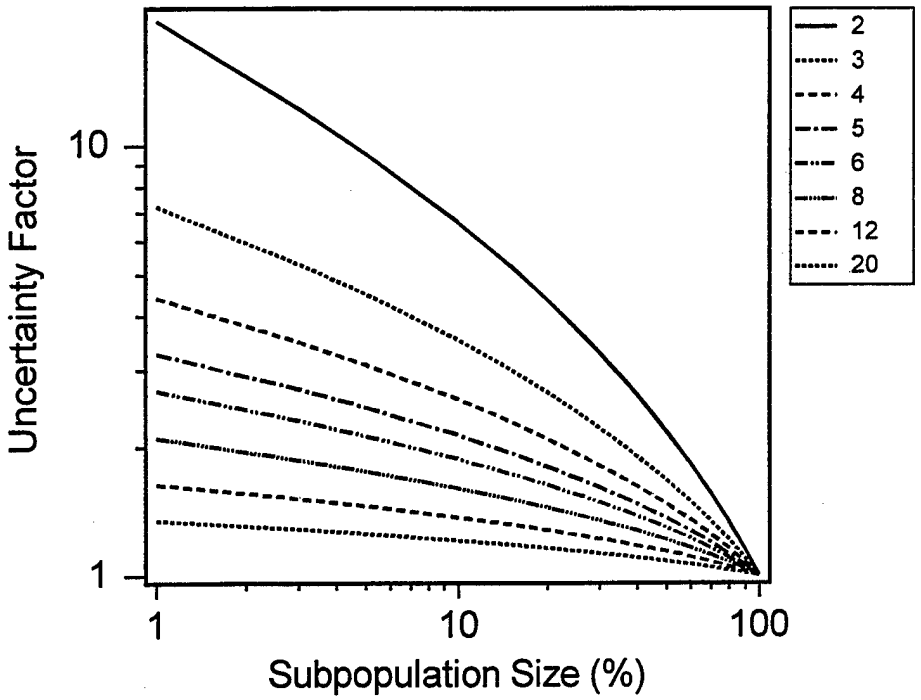


Table 5. Uncertainty Factors for Median — Tail Model

Subpop. Size (%)	Probit (Bliss) Slope of the General Population							
	2	3	4	5	6	8	12	20
1	19.41	7.22	4.41	3.28	2.69	2.10	1.64	1.35
3	12.16	5.29	3.49	2.72	2.30	1.87	1.52	1.28
5	9.55	4.50	3.09	2.47	2.12	1.76	1.46	1.25
10	6.64	3.53	2.58	2.13	1.88	1.61	1.37	1.21
15	5.25	3.02	2.29	1.94	1.74	1.51	1.32	1.18
20	4.37	2.67	2.09	1.80	1.64	1.45	1.28	1.16
25	3.76	2.42	1.94	1.70	1.56	1.39	1.25	1.14
30	3.30	2.22	1.82	1.61	1.49	1.35	1.22	1.13
35	2.93	2.05	1.71	1.54	1.43	1.31	1.20	1.11
40	2.64	1.91	1.62	1.47	1.38	1.27	1.18	1.10
45	2.39	1.79	1.55	1.42	1.34	1.24	1.16	1.09
50	2.17	1.68	1.47	1.36	1.30	1.21	1.14	1.08
60	1.83	1.50	1.35	1.27	1.22	1.16	1.11	1.06
70	1.56	1.34	1.25	1.19	1.16	1.12	1.08	1.05
80	1.34	1.22	1.16	1.12	1.10	1.08	1.05	1.03
90	1.16	1.10	1.08	1.06	1.05	1.04	1.02	1.02
100	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Figure 7. Uncertainty Factor for Median — Bell Model. Whole population probit slopes: 2, 3, 4, 5, 6, 8, 12, 20.

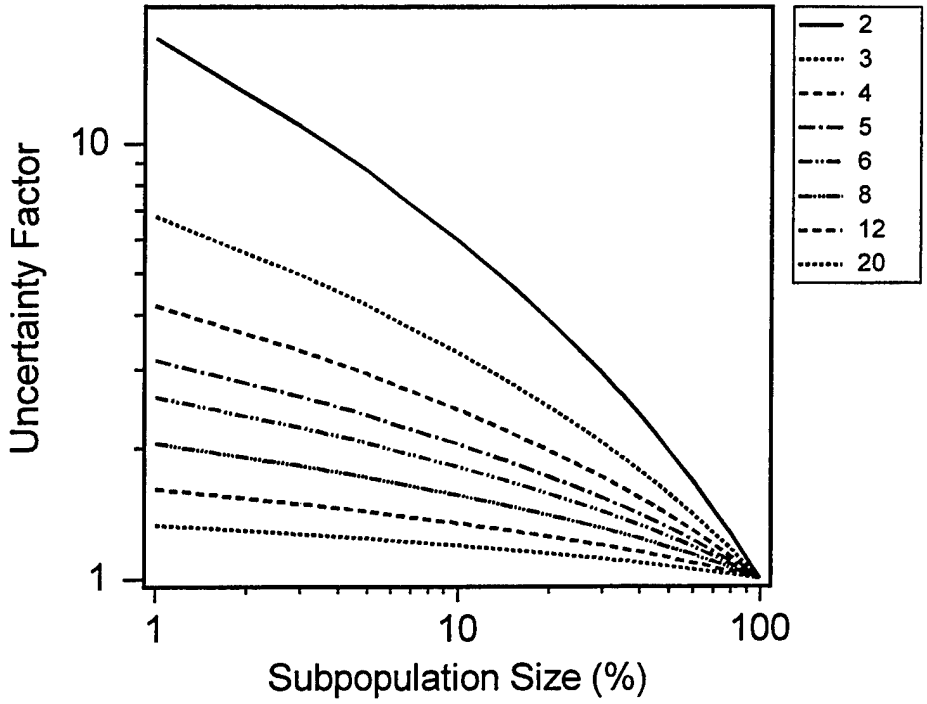


Table 6. Uncertainty Factors for Median — Bell Model

Subpop. Size (%)	Probit (Bliss) Slope of the General Population							
	2	3	4	5	6	8	12	20
1	17.73	6.80	4.21	3.16	2.61	2.05	1.61	1.33
3	11.05	4.96	3.32	2.61	2.23	1.82	1.49	1.27
5	8.63	4.21	2.94	2.37	2.05	1.71	1.43	1.24
10	5.99	3.30	2.45	2.05	1.82	1.56	1.35	1.20
15	4.72	2.81	2.17	1.86	1.68	1.47	1.30	1.17
20	3.93	2.49	1.98	1.73	1.58	1.41	1.26	1.15
25	3.38	2.25	1.84	1.63	1.50	1.36	1.23	1.13
30	2.97	2.07	1.72	1.55	1.44	1.31	1.20	1.12
35	2.65	1.91	1.63	1.48	1.38	1.28	1.18	1.10
40	2.39	1.79	1.54	1.42	1.34	1.24	1.16	1.09
45	2.17	1.68	1.47	1.36	1.29	1.21	1.14	1.08
50	1.98	1.58	1.41	1.32	1.26	1.19	1.12	1.07
60	1.69	1.42	1.30	1.23	1.19	1.14	1.09	1.05
70	1.46	1.29	1.21	1.16	1.13	1.10	1.07	1.04
80	1.28	1.18	1.13	1.10	1.08	1.06	1.04	1.02
90	1.13	1.08	1.06	1.05	1.04	1.03	1.02	1.01
100	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Table 7. Uncertainty Factors for 1st Percentile (Military to General) — Tail Model

Subpop. Size (%)	Probit (Bliss) Slope of the General Population							
	2	3	4	5	6	8	12	20
1	213.83	35.76	14.62	8.55	5.98	3.82	2.45	1.71
3	128.12	25.41	11.32	6.97	5.04	3.36	2.25	1.63
5	97.69	21.21	9.88	6.25	4.61	3.14	2.15	1.58
10	64.36	16.06	8.02	5.29	4.01	2.83	2.00	1.52
15	48.58	13.31	6.97	4.73	3.65	2.64	1.91	1.47
20	38.85	11.47	6.23	4.32	3.39	2.50	1.84	1.44
25	32.08	10.10	5.66	4.00	3.18	2.38	1.78	1.42
30	27.01	9.00	5.20	3.74	3.00	2.28	1.73	1.39
35	23.04	8.10	4.80	3.51	2.85	2.19	1.69	1.37
40	19.81	7.32	4.45	3.30	2.71	2.11	1.65	1.35
45	17.12	6.64	4.14	3.12	2.58	2.03	1.61	1.33
50	14.83	6.04	3.85	2.94	2.46	1.96	1.57	1.31
60	11.12	4.98	3.34	2.62	2.23	1.83	1.49	1.27
70	8.18	4.06	2.86	2.32	2.02	1.69	1.42	1.23
80	5.73	3.20	2.39	2.01	1.79	1.55	1.34	1.19
90	3.54	2.32	1.88	1.66	1.52	1.37	1.24	1.14
100	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Table 8. Uncertainty Factors for 1st Percentile (Military to General) — Bell Model

Subpop. Size (%)	Probit (Bliss) Slope of the General Population							
	2	3	4	5	6	8	12	20
1	100.73	21.65	10.04	6.33	4.65	3.17	2.16	1.59
3	54.85	14.44	7.41	4.96	3.80	2.72	1.95	1.49
5	39.37	11.57	6.27	4.35	3.40	2.50	1.84	1.44
10	23.53	8.21	4.85	3.54	2.87	2.20	1.69	1.37
15	16.53	6.49	4.07	3.07	2.55	2.02	1.60	1.32
20	12.49	5.38	3.53	2.75	2.32	1.88	1.52	1.29
25	9.81	4.58	3.13	2.49	2.14	1.77	1.46	1.26
30	7.95	3.98	2.82	2.29	2.00	1.68	1.41	1.23
35	6.53	3.49	2.56	2.12	1.87	1.60	1.37	1.21
40	5.46	3.10	2.34	1.97	1.76	1.53	1.33	1.18
45	4.61	2.77	2.15	1.84	1.66	1.47	1.29	1.17
50	3.92	2.49	1.98	1.73	1.58	1.41	1.26	1.15
60	2.91	2.04	1.70	1.53	1.43	1.31	1.19	1.11
70	2.18	1.68	1.48	1.37	1.30	1.22	1.14	1.08
80	1.67	1.41	1.29	1.23	1.19	1.14	1.09	1.05
90	1.29	1.18	1.13	1.11	1.09	1.07	1.04	1.03
100	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

From Grotte and Yang,[6] the LCT_{50} for inhalation of the CW agent GB (Sarin) vapor (exposure duration of two minutes) for a military population is given as 35 mg·min / m^3, with a probit slope of 12.

(a) Use θ_h = 25%.

(b) Obtain the probit slope of the general population from Tables 3 and 4. If θ_h equals 25%, then m_h / m_{whole} equals 2.03 (tail) or 1.66 (bell). Thus,

$$m_{whole} = (12 / 2.03) = 5.91 \text{ (tail)}$$

$$m_{whole} = (12 / 1.66) = 7.23 \text{ (bell)}$$

(c) From Tables 3 and 4, η_h = 1.15 (tail), or 1.06 (bell).

(d) Use equation [14] to calculate the UF for the median:

$$UF = \text{Antilog} (| \eta_{sub} | / m_{whole}) = \text{Antilog} (1.15 / 5.91) = 1.57 \text{ (tail)}$$

$$UF = \text{Antilog} (| \eta_{sub} | / m_{whole}) = \text{Antilog} (1.06 / 7.23) = 1.40 \text{ (bell)}$$

(e) Calculate LCT_{50} estimates for the general population:

$$LCT_{50} = 35 / 1.57 = 22 \text{ mg·min} / m^3 \text{ (tail)}$$

$$LCT_{50} = 35 / 1.40 = 25 \text{ mg·min} / m^3 \text{ (bell)}$$

Considering the precision of available data, there is little difference between the tail and bell model estimates for either m_{whole} or LCT_{50} (general).

4.2 COMPARISON WITH PREVIOUS WORK

We searched for studies having acute toxicity estimates for both the general population and a subpopulation. For these studies, we obtained uncertainty factors (between the subpopulation and general population) from the tail and bell models. Then we compared the uncertainty factors to ratios calculated from the median effective dosages reported in the studies.

4.2.1 US Coast Guard's Vulnerability Model

In developing a hazard assessment model [the Vulnerability Model (VM)] for the U.S. Coast Guard, Eisenberg *et al.*[25] addressed the inhalation toxicity of chlorine (Cl_2) and anhydrous ammonia (NH_3) in the context of performing casualty assessment (for both lethality and non-lethal effects) for the accidental release of these chemicals. Median effective dosages and probit slopes were needed in the VM for this purpose. In addition, Eisenberg *et al.*[25] also considered the issue of how to estimate the dose response curve of a high risk (sensitive) population that may be exposed to an accidental release.

Based on a review of accident data for both chlorine and ammonia, Eisenberg *et al.*[25] proposed (see their page 260) that the median lethal dosage for the sensitive population is located at the third percentile of the general population (or Z = -1.88). Furthermore, they

suggested that the sensitive population is comprised of (a) infants, (b) those over 70 years, and (c) others with advanced pulmonary/cardiovascular disease. Using demographic estimates compiled by Hewitt[69] (as reproduced in Withers and Lees[27]) for all three categories, we estimated the size of the Eisenberg *et al.* sensitive subpopulation to be 11%.

For chlorine, the probit slope for vapor concentration was estimated by Eisenberg *et al.*[25] to be 6.68 from non-lethal accident data involving the general population (see their Equation 6-4) and 10.7 from animal lethality data (see their Equation 6-2). Assuming that the laboratory animals were healthy young adults, we need to convert the estimate of 10.7 to a general population basis. This is done by using Table 4 and assuming that the size of the healthy subpopulation is 25% of the general population. Thus, the ratio of probit slopes (subpopulation / whole) is 1.66 (from the bell model), which converts 10.7 to 6.45. Averaging 6.68 and 6.45 gives 6.56.

Using [14] with η_s = -1.88 and m = 6.56, we calculate the chlorine uncertainty factor for the Eisenberg *et al.* toxicity estimates to be 1.93. From [8] (tail model) with θ_s = 11%, we find η_s = -1.60 and calculate the uncertainty factor (from [14]) to be 1.75 (for m = 6.56). An estimate of 1.70 is obtained from the bell model (Table 4). The average (1.73) obtained from the tail and bell models is about 10% less than the uncertainty factor calculated from [14] using the Eisenberg *et al.* toxicity estimates. Thus, there is good agreement between the uncertainty factors from the tail and bell models and the ratios calculated from the toxicity estimates of Eisenberg *et al.*

4.2.2 Withers and Lees (1985 and 1987)

Withers and Lees[26-28,68] investigated the inhalation toxicity of chlorine in the context of seeking to improve the prediction of human mortality resulting from chemical accidents. As part of their investigation, they addressed the issue of how toxicity differs for a vulnerable subpopulation in comparison to the general population.

Withers and Lees[27] treated the vulnerable and non-vulnerable (or regular) sections of the general population as separate distributions. In addition to the Eisenberg *et al.*[25] categories of sensitive individuals, children (ages 1 to 9 years) were also included by Withers and Lees.[27] Using the demographic work of Hewitt,[69] Withers and Lees[27] arrived at a rough estimate of 25% for θ_s. Obtaining any greater precision in this estimate was deemed by Withers and Lees[27] to be beyond the scope of their paper. Table 9 presents the Withers and Lees estimates of the XX% lethal concentrations (LC_{XX}) for 30-minute exposures for the vulnerable and non-vulnerable groups (assuming standard level of activity and inhalation rate of 12 L / min):[27,68]

The Withers and Lees LC_{XX} estimates for the regular subpopulation[27] were highly dependent on animal data (particularly dogs).[26] For the vulnerable subpopulation, Withers and Lees[27] based their estimates on the minimum concentration at which a human fatality has been observed and concentrations that are known to be intolerable or incapacitating for humans. This is similar to the approach proposed by Sommerville[70] for estimating CW agent threshold lethality via using the dosage required to achieve a severe sub-lethal effect among 16% of exposed individuals. Other researchers have recommended this type of approach for hazardous chemical exposures in general.[50,51,71] Withers and Lees[27] assumed that the probit slopes for the vulnerable and regular subpopulations were equal since there was no evidence to the contrary.

Table 9. Chlorine Toxicity Estimates from Withers and Lees (1985)

Group	LC_{50}	LC_{10}	Probit Slope	θ_{sub}
Vulnerable	100 ppm	50 ppm	4.25	25%
Regular	250 ppm	125 ppm	4.25	75%
Average	210 ppm	80 ppm	3.43*	100%

The Withers and Lees LC_{XX} estimates for the regular subpopulation[27] were highly dependent on animal data (particularly dogs).[26] For the vulnerable subpopulation, Withers and Lees[27] based their estimates on the minimum concentration at which a human fatality has been observed and concentrations that are known to be intolerable or incapacitating for humans. This is similar to the approach proposed by Sommerville[70] for estimating CW agent threshold lethality via using the dosage required to achieve a severe sub-lethal effect among 16% of exposed individuals. Other researchers have recommended this type of approach for hazardous chemical exposures in general.[50,51,71] Withers and Lees[27] assumed that the probit slopes for the vulnerable and regular subpopulations were equal since there was no evidence to the contrary.

The two subpopulation groups of Withers and Lees can be added together to form a general population curve that is only slightly skewed from normal with respect to log *C* (Figure 8). A direct calculation using the mixed distribution yields a probit slope of 3.43, and an LC_{50} of 207 ppm (compared to 210 ppm reported by Withers and Lees[27]), for the general population.

The ratio of the LC_{50} between the vulnerable subpopulation and the general population equals 210/100 or 2.1. Using the tail model (Table 3) with θ_s = 25% and m_{whole} = 3.43, we find the uncertainty factor to be antilog(| -1.15 | / 3.43) = 2.16; using the bell model (Table 4), we find the uncertainty factor to be 2.04.

The ratio of the LC_{50} between the regular subpopulation and the general population from Withers and Lees[27] equals 250/210 or 1.19. Using the tail model (Table 3) with θ_h = 75% and m_{whole} = 3.43, we find the uncertainty factor to be 1.24; using the bell model (Table 4), we find the uncertainty factor to be 1.20.

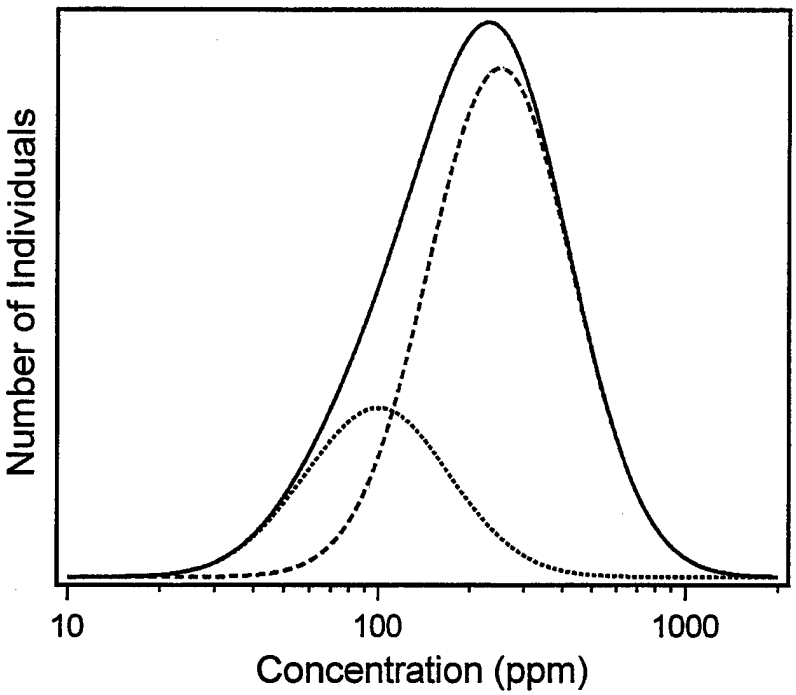
Our uncertainty factors for both subpopulations of Withers and Lees compare favorably with the ratios of the LC_{50} estimates from Withers and Lees. For both subpopulations of Withers and Lees, the bell model gave the best agreement with the LC_{50} ratios of Withers and Lees.

The ratio of probit slopes, m_{sub} / m_{whole}, from Withers and Lees[27] can be compared to the ratio of probit slopes obtained from the tail and bell models (Figure 5 or Tables 3 and 4). The ratio m_{sub} / m_{whole} from Withers and Lees for both regular and vulnerable subpopulations equals 4.25/3.43 or 1.24. For θ_{sub} = 75%, m_{sub} / m_{whole} equals 1.36 (tail model) or 1.14 (bell

* Value calculated by combining the vulnerable and regular groups from Withers and Lees.

model). For θ_{sub} = 25%, the slope ratio equals 2.03 (tail model) or 1.66 (bell model). The tail and bell models agree much better with the slope ratio for the regular subpopulation than with the slope ratio for the vulnerable subpopulation.

Figure 8. Chlorine Example. Whole population: solid line; vulnerable population: dotted line; non-vulnerable population: dashed line.



4.3 IMPLICATIONS FOR DEVELOPING AEGLs FOR CW AGENTS

Uncertainty factors to account for variability in the general human population (denoted as UF_{HV}) are used in the development of AEGLs. The AEGL SOP recommends (depending on the available data) using either 1, 3, or 10 (the default value) as the UF_{HV}. The goal is to be protective of the health of the sensitive subpopulation.

Using the tail and bell models, we calculated UF_{HV} values for CW agents for comparison to the UF_{HV} values used in draft CW agent AEGL documents.[68,72-75] We found in a review of the AEGL SOP[10] and representative CW agent AEGL documents[68,72-75] that the UF_{HV} was implicitly used to convert between the 1st percentiles of a healthy subpopulation and the general population. Thus, [13] was used to calculated UF_{HV} values (see Section 3.3) for comparison with the AEGL adopted values.

4.3.1 Estimation of General Population Probit Slopes for UF_{HV} Calculations

Estimation of θ_h for the military subpopulation was discussed in Section 2.4; θ_h was estimated to be 25% of the general population. Estimates for m_{whole} for CW agents were calculated from m_h by using Tables 3 and 4 with θ_h = 25%. The ratio m_h / m_{whole} equals 2.03 and 1.66, for the tail and bell models, respectively. Thus, m_h can be converted to corresponding m_{whole}. Estimates of m_h for lethality have recently been made for acute exposures of soldiers to

sulfur mustard (HD), G-type nerve agent, and the CW agent VX by inhalation (IH) or by percutaneous (PC) absorbtion.[6] Table 10 summarizes these m_h and their corresponding m_{whole}.

For two World War I era CW agents, phosgene (CG) and chlorine, m_h for lethality can be estimated from the references cited in draft AEGLs documents.[68,72] For phosgene, the rat lethality data of Zwart *et al.*[76] is cited as the basis for a threshold limit for lethality.[72] A probit analysis of the raw data from Zwart *et al.* (which were listed in the phosgene AEGL document[72]) gave a probit slope of 14.5. Converting this slope to a general population basis gives 14.5 / 2.03 = 7.14 (tail model) and 14.5 / 1.66 = 8.73 (bell model). The AEGL document[72] also cited the extensive literature review of Diller and Zante[77] on human phosgene exposures. Diller and Zante arrived at cumulative exposure estimates of 300 ppm·min and 500 ppm·min for the LCT_{01} and LCT_{50}, respectively. These estimates yield a probit slope of 10.5. We assume that the Diller and Zante data are from industrial accidents; hence, this slope (10.5) applies to a subpopulation of healthy workers. In 2000, the U.S. work force was about 50% of the population.[78,79] Withers and Lees[27] estimated the non-vulnerable subpopulation to be 75% of the population; their estimate is reasonable, given the exclusion of healthy homemakers, students, and prisoners from the workforce. However, we use 50% as the size of the healthy working population; doing so yields m_{whole} = 10.5 / 1.66 = 6.33 for the tail model and m_{whole} = 10.5 / 1.34 = 7.84 for the bell model. Thus, the average m_{whole} estimates for phosgene are (7.14 + 6.33) / 2 = 6.74 for the tail model and (8.73 + 7.84) / 2 = 8.28 for the bell model.

Table 10. Comparison of Intraspecies Uncertainty Factors

Agent	Route	Military Probit Slope	m_{whole}		Uncertainty Factors (Between 1st Percentiles)		
			Tail	Bell	Tail	Bell	Draft AEGL
G	IH	12.0	5.9	7.2	3.2	1.9	10
G	PC	5.0	2.5	3.0	16.7	4.6	
HD	IH	6.0	3.0	3.6	10.4	3.6	3
HD	PC	7.0	3.4	4.2	7.5	3.0	
VX	IH	6.0	3.0	3.6	10.4	3.6	10
VX	PC	6.0	3.0	3.6	10.4	3.6	
CG	IH		6.7	8.3	2.8	1.7	3
Chlorine	IH		5.9		3.2	2.2	3

For chlorine, there are several probit slope estimates for inhalation lethality for the general population, m_{whole}, that have been summarized in two sources [slopes have been recalculated as needed to give the probit slope with respect to log(*C*)]: [27,52]

3.2 (ten Berge and van Heemst)[53]

3.4 (Withers and Lees--see Section 4.2.2)[27]

5.2 (Harris and Moses)[80]

6.5 (Eisenberg *et al.* (lethal)--see Section 4.2.1)[25]

6.7 (Eisenberg *et al.* (non-lethal)--see Section 4.2.1)[25]

7.2 (Perry and Articola--calculated via probit analysis of data listed in the third table of their page C-5)[81]

The median of these estimates is 5.85, which will be used as m_{whole} for chlorine in this discussion. Table 10 summarizes estimates of m_{whole} for chlorine and other CW agents.

4.3.2 Calculation of UF_{HV}

Once estimates of m_{whole} were collected for the above CW agents, The UF_{HV} values were calculated using [13]. The UF_{HV} accounts for the difference between $\Psi(01)_h$ and $\Psi(01)_{whole}$ (see Section 4.3). We used θ_h = 25%, which is appropriate for healthy military personnel. Using θ_h = 25% yields $\Psi(01)_h$ = 0.68 for the tail model (Table 3) and $\Psi(01)_h$ = – 0.34 for the bell model (Table 4). Thus, [13] reduces to:

$$UF_{HV}\text{ (tail model)} = \text{antilog}\left(|0.68 - (-2.33)| / m_{whole} \right) = \text{antilog}\left(3.01 / m_{whole}\right)$$

$$UF_{HV}\text{ (bell model)} = \text{antilog}\left(|(-0.34) - (-2.33)| / m_{whole} \right) = \text{antilog}\left(1.99 / m_{whole}\right)$$

Table 10 gives the calculated UF_{HV} values, along with the UF_{HV} values that were used in the proposed AEGLs.

4.3.3 UF_{HV} Used in Proposed AEGLs

The AEGL UF_{HV} values listed in Table 10 come from values identified in the AEGL documents[68,72-75] as a human intraspecies uncertainty factor to account for sensitive individuals in the development of AEGL-3* values (threshold lethality). The UF_{HV} is implicitly used to convert a threshold lethality for a healthy subpopulation to a threshold lethality for a sensitive subpopulation. The AEGL-3 values[68,72-75] for the CW agents are based on the inhalation (IH) route of exposure, since this is the most toxic route. Thus, the AEGL UF_{HV} values are only meant for IH exposures, and no corresponding AEGL UF_{HV} for percutaneous (PC) exposures exist. Table 10 has probit slope values and calculated human intraspecies UF_{HV} values for both IH and PC exposures using the tail and bell models.

4.3.4 Comparison of UF_{HV} Values from Present Method with AEGL UF_{HV} Values

The agreement between the UF_{HV} values given by the tail and bell models increases as m_{whole} increases. This is seen in contrasting those agents with good agreement (high probit slope groups: G-agent, CG and Chlorine) and poor agreement (low probit slope groups: VX and HD) between the tail and bell models (Table 10). Being more conservative (see Section 2.3.3), the tail model provides larger UF_{HV} values than the bell model.

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* There are three levels of AEGLs: AEGL-1 (threshold notable discomfort), AEGL-2 (threshold serious effects) and AEGL-3 (threshold lethality). Refer to AEGL documents[10,68,72-75] for more detailed definitions of the individual levels.

The tail model provides the best agreement with the AEGL IH UF_{HV} values (Table 10) for VX, CG and Chlorine. The bell model provides the best agreement with the values for HD. Neither the tail or bell model UF_{HV} values are in agreement with the G-agent AEGL value, both models providing significantly lower values (3.2 and 1.9, respectively) than the AEGL UF_{HV} value of 10.

The AEGL UF_{HV} values for VX, CG and Chlorine may be too conservative, based upon the agreement between these values and the tail model predictions, which are the upper limit for what the UF_{HV} can be. Values from the bell model may be more appropriate for use with these agents.

5. SUMMARY

A method has been developed for converting existing human CW agent toxicity estimates (both median effective dosage and probit slope) from a healthy subpopulation basis to a general population basis. Only three items of subpopulation information are required for using the method: median effective dosage, probit slope, and subpopulation size (as a fraction of the general population). Prior to this report, the conversion of probit slopes had not been rigorously explored.

The new method addresses a critical parameter gap (general population CW agent toxicity estimates) in transport & dispersion and hazard assessment models. The existing median CW agent dosages and probit slopes were developed for 70 kg male military personnel and are not appropriate for use in CW agent release scenarios involving the general population.

The new method is based on the mathematical modeling of a subpopulation and its relationship to the whole population. This permits the quantitative estimation of the difference between the median effective dosages and between the probit slopes of the two populations. Both healthy and sensitive subpopulations can be modeled, and modifications for gender effects were addressed. Two subpopulation models (tail and bell models) were developed, and both produced similar trends of LD50 and probit slope as a function of subpopulation size.

Historical military demographics were investigated to obtain an estimate of the size of the healthy subpopulation from which military personnel are drawn. In addition, a short review was made of previous attempts to quantify the size of the sensitive subpopulation. Uncertainty factors calculated using the new method were consistent with two previous studies that quantified differences between subpopulations.

Lastly, a demonstration was made of the new method's application towards the derivation of an intraspecies UF for deriving AEGLs. Both subpopulation models (tail and bell) were used to estimate intraspecies UFs for comparison with the qualitative intraspecies AEGL UFs adopted for CW agents. For G-agents, UFs from both the tail and bell models are significantly lower than the AEGL UF. For the other agents reviewed (HD, VX, CG and Chlorine), the comparison results from the tail and bell models are mixed. As a result of this demonstration, a strong argument exists for the current AEGL intraspecies UF for G-agents being too high. Furthermore, the current AEGL intraspecies UF for VX is questionable.

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NOMENCLATURE

a	Location of Border of Tail Subpopulation
AEGL	Acute Exposure Guideline Level
AEGL-X	Acute Exposure Guideline Level X (X = 1, 2 or 3)
Bell	Normal distribution (the bell-shaped curve)
C	Concentration
CG	phosgene (CW choking agent)
CW	Chemical Warfare
ECT_{XX}	Effective Concentration-Time for XX% of Individuals
ED	Effective Dosage
ED_{XX}	Effective Dosage for XX% of Individuals
G( )	Inverse Cumulative Distribution Function of a Standard Normal
G-agent	G series of CW nerve agents
GB	sarin (CW nerve agent)
HD	sulfur mustard (CW blister agent)
IH	Inhalation Exposure
k	Fitted coefficients for Probit Analysis/MLE (in [4])
LC_{XX}	Lethal Concentration for XX% of Exposed Individuals
LCT_{XX}	Lethal Concentration-Time for XX% of Exposed Individuals
m	Probit (or Bliss) Slope
n	Toxic Load Exponent
PC	Percutaneous Exposure
SOP	Standard Operating Procedure
T	Exposure Time
UF	Uncertainty Factor
UF_{HV}	Uncertainty Factor to Account for Variability in the General Human Population

VX	CW nerve agent
X	Unstandardized Normally Distributed Variable
Y_N	Normit
Y_P	Probit
Z	Standard Normal Random Variable

GREEK SYMBOLS

$\Phi(Z)$	Probability Density Function of a Standard Normal (pdf)
η	Median (Equivalent to $\Psi(50)$)
μ	Mean
θ	Size of Subpopulation (as a Fraction of the Whole Population)
σ	Standard Deviation
$\Psi(XX)$	XX Percentile

SUBSCRIPTS

bell	Bell Model
centroid	parameter associated with centroid of some region
h	Healthy Subpopulation
hf	Healthy Subpopulation (female)
hm	Healthy Subpopulation (male)
max	maximum
s	Sensitive Subpopulation
sub	Subpopulation
tail	Tail Model
whole	Whole Population